REMARKS

Claims 13, 17, and 19-42 are pending in the application. Claims 13, 17, and 19-38 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 39-42 are currently being examined on the merits.

Withdrawal of previous rejections and objections

Applicants thank the Examiner for withdrawing the rejections under 35 U.S.C. § 102, and believe that based on the remarks made herein, the remaining rejections and objections should also be withdrawn.

Utility rejections under 35 U.S.C §§ 101 and 112, first paragraph:

Claims 39-42 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as allegedly lacking either a substantial, specific asserted utility or a well established utility. In particular, the Examiner asserts that "neither the specification nor any art of record demonstrates a correlation between the overexpression of SCAH-2 or lack thereof and the presence of a pathophysiological disease state" (Office Action, p. 3). The Examiner also asserts that "the function of the SEQ ID NO:2 polypeptide could not be anticipated" based upon alleged difficulties in using sequence homology to predict protein function. **The rejection of claims 39-42 is improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.**

The invention at issue, identified in the patent application as SCAH-2, is a polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a member of the class of Ly-6 stem cell antigens, whose biological functions include roles in the maturation of T and B cells, regulation of interleukin 12 secretion, and involvement in a highly malignant phenotype of tumor cells (Au-Young '080 application at, for example, pp. 1-2). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide

actually functions. Furthermore, SCAH-2 is expressed in tissues derived from cancer, in particular, from bladder tumor tissue (Au-Young '080 application, p. 5, lines 23-25, and p. 32, lines 4-11), and thus may serve as a tumor marker. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The similarity of the claimed polypeptide to other polypeptides of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. SCAH-2 is, in that regard, homologous to the known stem cell antigen, chicken stem cell antigen 2 (GI 509840; SEQ ID NO:20). In particular, SCAH-2 has 27% amino acid identity with chicken stem cell antigen 2 (Au-Young '080 application, p. 6, lines 10-12). In addition, it is well known in the art that the members of the Ly-6 family contain 10 conserved cysteine residues (see the Classon article, Tab H, p. 5297, col. 2, and Figure 3A). As shown in Figure 3 of the specification, SCAH-2 conserves all 10 of these characteristic cysteine residues as well as the conserved N-linked glycosylation site at N93 (see also Au-Young '080 application, page 6, lines 15-19). The C-terminus of SCAH-2 is enriched in hydrophobic amino acids as shown in a hydrophobicity plot for SCAH-2 (Au-Young '080 application, Figure 5), also characteristic of Ly-6 family members, which have C-terminal hydrophobic signal sequences for GPI attachment (Classon, Tab H, p. 5298, col. 1). This is more than enough homology to demonstrate a reasonable probability that the utility of the Ly-6 stem cell antigen family can be imputed to the claimed invention.

The fact that the claimed polypeptide is a member of the Ly-6 stem cell antigen family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polypeptide also has patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this brief the Declaration of Lars Michael Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed

polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 12).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polypeptides for diagnosis of conditions or diseases characterized by expression of SCAH-2, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The claimed polypeptide's membership in the Ly-6 stem cell antigen family demonstrates utility

Because there is a substantial likelihood that the claimed SCAH-2 is a member of the family of polypeptides known as the Ly-6 stem cell antigens, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1560, 1566.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:2 in the patent application and referred to as SCAH-2 in that application. Applicants have demonstrated by more than reasonable probability that SCAH-2 is a member of the Ly-6 stem cell antigen family, and that the Ly-6 stem cell antigen family of proteins includes proteins with expression levels that are correlated to cancers and immune disorders (Au-Young '080 application, pp. 1-2). For example, the Katz article discloses that high expression of Ly-6 in non-lymphoid tumor cells is linked to a highly malignant phenotype (Tab I, p. 690). Antibodies to Ly-6 were found to transduce proliferation (Tab I, pp. 688-689). The Blake article discloses that injections with recombinant interferon gamma markedly increased the expression of Ly-6 (Tab J, p. 1144, col.2). Expression of Ly-6 was also upregulated in murine lupus nephritis and in mercuric chloride neuropathy, diseases in which interferon gamma is known to play a role (Tab J, p. 1145).

SCAH-2 has 27% amino acid identity with chicken stem cell antigen 2 (Au-Young '080 application, p. 6, lines 10-12). In addition, it is well known in the art that the members of the Ly-6 family contain 10 conserved cysteine residues (see the Classon article, Tab H, p. 5297, col. 2, and Figure 3A). As shown in Figure 3, SCAH-2 conserves all 10 of these characteristic cysteine residues as well as the conserved N-linked glycosylation site at N93 (see also Au-Young '080 application, page 6, lines 15-19). The C-terminus of SCAH-2 is enriched in hydrophobic amino acids as shown in a hydrophobicity plot for SCAH-2 (Au-Young '080 application, Figure 5), also characteristic of Ly-6 family members, which have C-terminal hydrophobic signal sequences for GPI attachment (Tab H, p. 5298, col. 1). In addition, Applicants have previously submitted BLAST results of SCAH-2 against the Genpept database (Exhibit A, submitted with the Response to Office Action filed May 7, 2001) which show that all of the ten hits which have known functions are stem cell antigens. Thus, there is no reason for one of ordinary skill in the art to believe that SCAH-2 is not in fact a stem cell antigen.

Applicants also respectfully point out that, as disclosed in the specification, the sequence encoding SCAH-2 was first isolated from a bladder tumor cDNA library (specification, page 6, lines 29-33), the preparation of which is described in the specification in Example I (page 32). This evidence indicates an association of SCAH-2 expression with cancer.

Furthermore, Applicants have previously (in the Response to Office Action mailed May 7, 2001) submitted a post-filing reference, Reiter et al., that discloses a protein having an amino acid sequence with 99% identity to SEQ ID NO:2 (differing only at the position of the "X" residue in SEQ ID NO:2), referred to as prostate stem cell antigen (PSCA). Like the other members of the Ly-6 family, PSCA is a GPI-anchored glycoprotein expressed on the cell surface (Reiter, page 1738). PSCA is predominantly prostate-specific in normal tissues and is overexpressed in over 80% of prostate cancers (Reiter, page 1739, column 1). This reference thus confirms Applicants' conclusions that SCAH-2 is a Ly-6 stem cell antigen and demonstrates the validity of predicting protein function based upon structural homologies. This data also confirms that SEQ ID NO:4 is in fact translated into the polypeptide of SEQ ID NO:2, and that this polypeptide is associated with cancers.

The Examiner asserts that the reference by Reiter et al. "represents information that was not available at the time of the instant invention, as the specification does not discuss SEQ ID NO:2 as a

prostate stem cell antigen or the use of SEQ ID NO:2 in a diagnostic or therapeutic method" (Office Action, p. 8). The Examiner's attention is respectfully directed to the specification at page 24, lines 14-18 ("The polynucleotides disclosed herein may be useful in the treatment of conditions associated with the tissues used to construct the cDNA libraries (shown in the Sequence ID Listing) which contained partial scah sequences. These include, but are not limited to, conditions such as leukemias and cancers of the bladder, breast, lung, ovary, prostate and uterus.") Thus the association of SCAH-2 with prostate cancer, as well as other specific cancers, was disclosed in the specification.

Applicants also note that the association of SCAH-2 with tumors and the use of SCAH-2 in screening, diagnosis and treatment of cancers was asserted in the specification at, for example, page 3, lines 9-14, and page 18, lines 12-17 wherein the specification states that "[s]ince a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and a more malignant phenotype, the SCAH-1 and SCAH-2 proteins can be used to identify antibodies, antagonists, and inhibitors which would diminish the efficiency of local tumor growth without inducing cell proliferation." Methods for diagnostic assays and drug screening are disclosed in the specification at, for example, pages 20-21. The specification further discloses that "a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and with a more malignant phenotype" (page 18, lines 12-13).

Thus, in contrast to the assertions of the Examiner (Office Action, pp. 6-7), the specification discloses specific diseases to be diagnosed, specific body tissues, and the expected change in expression levels associated with disease diagnosis. The teachings of Reiter et al. that PSCA is useful in the diagnosis of prostate cancer merely confirms the utilities in screening, diagnosis and treatment of cancers which were asserted by the applicants at the time of filing.

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of the Ly-6 stem cell antigen family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the Ly-6 stem cell antigen family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the Ly-6 stem cell antigen family, useful.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function (Office Action, pp. 3-5), none suggest that functional homology cannot be inferred by a reasonable probability in this case. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Furthermore, many of these articles do not support the points which the Examiner intends to make. The claimed SCAH-2 polypeptide, having the amino acid sequence of SEQ ID NO:2, was identified as a stem cell antigen in part due to chemical and structural homology with other known stem cell antigens. While acknowledging that SCAH-2 shares 27% amino acid sequence identity with chicken stem cell antigen-2, the Examiner attaches great significance to the fact that the sequences also show a 73% dissimilarity. The Examiner argues that Bowie et al. teach that certain positions of a protein sequence are critical to the three-dimensional structure and function of the protein and therefore can tolerate only conservative substitutions or no substitutions (Office Action, p. 4). Applicants respectfully direct the Examiner's attention to Bowie et al. at page 1306, column 2, wherein the authors state that "proteins are surprisingly tolerant of amino acid substitutions," and that "at some positions, many different nonconservative substitutions were allowed." It is well-known in the art that natural selection tends to conserve those residues critical for protein structure and function during the course of evolution. This is why the study of a set of related sequences can indicate which residues are critical, since these are the ones which are conserved between sequences of different species (See Bowie et al., page 1306, and pages 1308-1309).

For example, in the case of the Ly-6 family proteins it is well known in the art that the members of this family contain 10 conserved cysteine residues (R.G.E. Palfree "Ly-6-domain proteins - new insights and new members: a C-terminal Ly-6 domain in sperm acrosomal protein SP-10" Tissue Antigens (1996) 48:71-79; art of record). As shown in Figure 3, SCAH-2 conserves all 10 of these

characteristic cysteine residues (see also the specification, page 6, lines 15-19). While the number and spacing of the 10 cysteine residues is characteristic of the family, "they provide a framework for considerable sequence diversity among the relatives" (Palfree, page 72, col. 1). SCAH-2 also conserves the characteristic N-linked glycosylation site at N93 (Classon article, Tab H, p. 5297, col. 2, and Figure 3A; and Au-Young '080 application, Figure 3). Furthermore, the C-terminus of SCAH-2 is enriched in hydrophobic amino acids as shown in a hydrophobicity plot for SCAH-2 (Au-Young '080 application, Figure 5), also characteristic of Ly-6 family members, which have C-terminal hydrophobic signal sequences for GPI attachment (Classon article, Tab H, p. 5298, col. 1). Thus the Examiner has provided no reason why one of skill in the art would not believe that the 27% amino acid identity between SCAH-2 and chicken stem cell antigen-2, (a level of identity similar to that between other family members, as shown in Figure 1 of Palfree), together with the presence of the conserved cysteine residues, N-linked glycosylation site, and C-terminal hydrophobic sequence, would in fact be sufficient to conserve the structural and functional properties between the two proteins.

The other examples cited by the Examiner, Burgess et al. and Lazar et al., fail to provide support for the Examiner's position, since both discuss the effects of artificial, site-directed mutations of residues selected in the belief that they were essential for protein function. Indeed, the sites for mutation in Lazar et al. were specifically chosen based upon the fact that "these two amino acids are highly conserved in the EGF-like family of peptides" (Lazar et al., page 1247, col. 1). It is hardly surprising that these amino acid substitutions had significant effects on protein function, but such mutations are precisely those that would be selected against during the course of evolution. Applicants note, for instance, that while the family of EGF-like peptides shares only about 35% amino acid homology (Lazar et al., page 1247, col. 1) the two amino acids found by Lazar et al. to be important for protein function were highly conserved across the entire family. The examples cited by the Examiner are therefore irrelevant to the question of whether a naturally-occurring sequence retains the function of its homolog, as is the case here.

The Examiner also relies upon the paper by Bork, to argue that sequence analysis of SCAH-2 cannot be used to reliably predict the protein's function. Applicants respectfully suggest that the Examiner attempts to draw too sweeping conclusions from Bork. It may be true that the use of

sequence analysis to predict protein function is not 100% percent accurate (although still, based upon Bork's figure of 70% accuracy, more likely than not to be correct) as the quality of data in the public sequence databases is still insufficient to perfectly annotate every new sequence. However, this is a general conclusion; one of skill in the art would clearly understand that the likelihood of a prediction being correct for a particular sequence depends upon how much data is available for the particular family to which it belongs. As discussed in Bowie et al. "[t]here is more information in a set of related sequences than in a single sequence" (page 1309, col. 2). As discussed above, there is ample evidence that SCAH-2 shares the conserved properties of the Ly-6 family of related sequences.

B. The use of SCAH-2 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. These techniques are well established in the art, as discussed in greater detail below.

The instant application is a divisional of, and claims priority to, United States patent application Serial No. 08/675,508 filed on July 3, 1996 (hereinafter "the Au-Young '508 application").

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Au-Young '508 application on July 3, 1996 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-12). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Au-Young '508 application . . . and other related pre-July 1996 publications, persons skilled in the art on July 6, 1996 clearly would have understood the Au-Young '508 application to disclose the SEQ ID NO:2 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶ 10)
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> * * *
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> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:2 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancers and immune disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, form the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (reference 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656.)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (reference 2); and Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (reference 3).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See the enclosed email (reference 4) from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these

databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific, substantial, and credible" utilities (Office Action, p. 2). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological significance" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results ("some expression pattern") generated in any given expression analysis (Office Action, p. 6).

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptide is a member of the Ly-6 stem cell antigen family, whose members indisputably are useful, the Examiner refused to impute the utility of

the members of the Ly-6 stem cell antigen family to SCAH-2. In the Examiner's Answer, the Patent Examiner takes the position that unless Applicants can identify which particular biological function within the class of Ly-6 stem cell antigens is possessed by SCAH-2, such as the particular organs or tissue types which harbor stem cells in which SCAH-2 is expressed, utility cannot be imputed (Office Action, p. 6). To demonstrate utility by membership in the class of Ly-6 stem cell antigens, the Examiner would in effect require that all Ly-6 stem cell antigens possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses SCAH-2 as if the general class in which it is included is not the Ly-6 stem cell antigen family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the Ly-6 stem cell antigen

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

family does not. The Ly-6 stem cell antigen family is sufficiently specific to rule out any reasonable possibility that SCAH-2 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the Ly-6 stem cell antigen family has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed SCAH-2 also is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the Ly-6 stem cell antigen family would meet it. It is undisputed that known members of the Ly-6 stem cell antigen family are proteins which are expressed on the surface of stem cells and are involved in a highly malignant phenotype of tumor cells (Au-Young '080 application at, for example, p. 1, line 35 through p. 2, line 3). A person of ordinary skill in the art need not know any more about how the claimed invention regulates the malignancy of tumor cells to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given Ly-6 stem cell antigen is expressed in a specific tissue or is correlated with a specific cancer (Final Office Action, p. 6). The Examiner then goes on to assume that the only use for SCAH-2 absent knowledge as to how the Ly-6 stem cell antigen actually works is further study of SCAH-2 itself (Office Action, p. 7).

Not so. As demonstrated by Applicants, knowledge that SCAH-2 is a human stem cell antigen is more than sufficient to make it useful for the diagnosis and treatment of cancers and immune system disorders. Indeed, SCAH-2 has been shown to be expressed in tissues derived from cancers, including bladder tumors (Au-Young '080 application, p. 6, lines 29-33, and p. 32). The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The use of SCAH-2 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The PTO's rejection of the claims is tantamount to a declaration that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility". These include use of the claimed polypeptide sequences

and the polynucleotides which encode them in disease diagnosis, expression profiling, and drug discovery (Au-Young '080 application, p. 18, lines 7-17; p. 20, lines 5-19; p. 20, line 32 though p. 21, line 17; and pp. 21-24).

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its homology to other polypeptides undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.A., *supra*, the literature cited by the Examiner is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised

Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of

utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first

paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Enablement rejections under 35 U.S.C.§ 112, first paragraph:

Claims 39 and 41 are also rejected under 35 U.S.C.§ 112, first paragraph for alleged lack of enablement of the claimed variants and fragments of SEQ ID NO:2. The Examiner asserts that "the specification does not reasonably provide enablement for amino acid sequences having 90% sequence identity to SEQ ID NO:2, wherein the sequences are expressed on the surface of stem cells, biologically active fragments of SEQ ID NO:2, wherein said fragments are expressed on the surface of stem cells or immunogenic fragments of SEQ ID NO:2" (Office Action, p. 9).

With respect to variants of SEQ ID NO:2, the Examiner asserts that "the specification does not provide a written description of the amino acid sequences of the claimed variants to SEQ ID NO:2" and that one of skill in the art would not know "the organ or tissues harboring said stem cells in order to isolate said cells and determine the sequence of the variant polypeptide" (Office Action, pp. 9-10). Applicants respectfully note that the Examiner has not made a rejection for lack of adequate written description, but for lack of enablement. "Variants" of SCAH-2 are disclosed in the specification at, for example, p. 4, lines 25-24, and p. 10, lines 26-34. Applicants further note that the specification does identify specific tissues in which scah sequences were found to be expressed, including bladder, breast, lung, ovary, prostate and uterus (Au-Young '080 application, p. 24, lines 14-18). Thus one of ordinary skill in the art would be able to determine the bodily tissues from which to isolate the stem cells without any undue experimentation.

Furthermore, assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, page 38, lines 10-12. The specification has also disclosed residues which are conserved across a number of stem cell antigens and thus likely to be important for function, for example, the conserved cysteine residues (Au-Young '080 application, p. 6, lines 15-19). Thus the skilled artisan would have additional guidance in making and using the claimed variants.

With respect to the claimed biologically active fragments, the Examiner asserts that "the specification does not provide a written description of the portion of SEQ ID NO:2 that is exposed on the cell surface" (Office Action, p. 10). Applicants again note that the Examiner has not made a rejection for lack of adequate written description, but for lack of enablement. Fragments of SCAH-2 are disclosed in the specification as being useful for the generation of antibodies, or in various drug screening techniques (Au-Young '080 application, p. 18, lines 23-27, and p. 20, line 32 through p. 21, line 13). It is not necessary for the specification to list the sequences of all the biological fragments encompassed by the claims, since one of ordinary skill in the art would be able to identify and use those biologically active fragments retaining the required activity by following the guidance in the specification, without any undue experimentation.

Applicants also note that it is well-known in the art that members of the Ly-6 stem cell antigen family are anchored to the cell membrane by a GPI anchor (Au-Young '080 application, p. 1, lines 11-13). Ly-6 family members are known to have C-terminal hydrophobic signal sequences for GPI attachment (Classen, Tab H, p. 5298, col. 1). The C-terminus of SCAH-2 is enriched in hydrophobic amino acids as shown in a hydrophobicity plot for SCAH-2 (Au-Young '080 application, Figure 5), indicating that it too contains this characteristic C-terminal hydrophobic sequence. Thus one of ordinary skill in the art would reasonably expect that a SCAH-2 fragment that included this region would be expressed on the surface of stem cells. Specific tissues in which scah sequences were found to be expressed, including bladder, breast, lung, ovary, prostate and uterus, are identified in the specification (Au-Young '080 application, p. 24, lines 14-18). In addition, assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, page 38, lines 10-12, providing the skilled artisan with additional guidance in making and using those biologically active fragments recited by the claims.

With respect to the claimed immunologically active fragments, the Examiner asserts that the specification does not teach any examples of immunologically active fragments. The Examiner further asserts that "[t]he determination of an immnogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 polypeptide which have been determined to be immunogenic fragments in a specific organism, it would require

undue experimentation for one of skill in the art to make and use the invention as claimed" (Office Action, p. 12).

Applicants respectfully point out that the generation of antibodies to proteins is well known in the art and is routinely successful without knowledge of the three dimensional structure of the protein, in contrast to the assertions of the Examiner (Office Action, p. 12). In addition, the specification provides further guidance as to the selection of immunogenic fragments. See, for example, page 38, lines 15-21, wherein the specification describes software programs used to determine regions of high immunogenicity and also discloses that appropriate epitopes may include "those near the C-terminus or in hydrophilic regions." A hydrophobicity plot for SCAH-2 is provided in Figure 5.

Applicants note that Paul et al., a reference cited by the Examiner, concurs that "hydrophilicity has been proposed as a second indication of immunogenicity" and that of 12 proteins tested, "the most hydrophilic site of each protein was indeed one of the antigenic sites" (Paul et al., page 249). Thus even the evidence cited by the Examiner confirms that based upon the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:2 without any undue experimentation.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph:

Claims 39-42 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner asserts that the recitation of "biologically active fragments" is vague and indefinite, because the specification defines "biologically active" as having structural, regulatory or biochemical functions of the naturally occurring SCAH, but there is allegedly no description of what constitutes these functions (Office Action, p. 13).

Applicants respectfully point out that in determining if the claims are indefinite, the Examiner must first look to the language of the claims themselves. Claim 39 recites "a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment is expressed on the surface of stem cells." Thus the biological activity of the claimed fragments is clearly

stated in the claim itself to be expression on the surface of stem cells. This is not in any way inconsistent with the definition provided in the specification. The specification has already made clear that one of the functions of naturally occurring SCAH is expression on the surface of stem cells ("the invention features substantially purified SCAH-1 and SCAH-2, encoded by the amino acid sequences of SEQ ID NO:1 and 2, respectively, and having characteristics of the LY-6 family of cysteine rich proteins which are expressed on the surface of stem cells" (Au-Young '080 application, p. 2, lines 21-24)). Thus one of ordinary skill in the art would clearly understand what is encompassed by the claims.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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